

## Regional blood flow correlates of ST segment depression in tachycardia-induced myocardial ischemia

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**ABSTRACT** Tachycardia produces subendocardial ischemia and ST segment abnormalities after coronary obstruction. To determine whether a quantitative relationship exists between these ST shifts and transmural blood flow, 19 dogs were studied. Coronary obstruction was produced by ameroid constriction of the left circumflex artery, and tachycardia was generated by atrial pacing at 90 to 210 beats/min. ST shifts were studied by body surface isopotential mapping with an 84-electrode torso grid, and blood flow was quantitated by serial radiolabeled microsphere injections. Isopotential maps at each paced rate, 40 msec into the ST segment, were classified as normal or ischemic based on spatial patterns of voltages. Pacing after 3 weeks of ameroid constriction reduced endocardial/epicardial flow ratios in 11 dogs from  $1.16 \pm 0.22$  at rest to  $0.41 \pm 0.18$  at 210 beats/min. Abnormal ST depression developed in these dogs at a rate of  $184.0 \pm 16.5$  beats/min. Endocardial/epicardial ratios with ST depression ( $0.45 \pm 0.15$ ) were lower than at those without ST depression ( $1.05 \pm 0.19$ ;  $p < .01$ ). Logistic regression analysis demonstrated that ST depression corresponded to an endocardial/epicardial ratio of 0.67 or less ( $p < .01$ ). With this model, 95.5% of data sets were correctly classified. Neither heart rate nor perfusion bed size were significant independent predictors of an ischemic electrocardiographic response. The magnitude of abnormal ST segment shift was significantly correlated ( $r = .87$ ) with the transmural flow ratio. Thus (1) development of electrocardiographic changes indicative of ischemia corresponds to a predictable degree of flow redistribution and (2) the magnitude of the ST shift is correlated with the intensity of the flow abnormality.

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ELECTROCARDIOGRAPHIC changes provoked by exercise<sup>1</sup> or by atrial pacing<sup>2</sup> are commonly used clinical criteria for detecting significant coronary artery obstruction. Reliance on ST segment shifts is predicated on the concept that the resulting tachycardia produces subendocardial ischemia in the presence of arterial disease.<sup>3-4</sup> This in turn reverses the normal transmural gradient of ventricular repolarization properties<sup>5</sup> to effect diagnostic changes in the electrocardiogram.<sup>6</sup>

Although shifts in myocardial blood flow during tachycardia have been documented in animal<sup>3, 4, 7, 8</sup> as well as in clinical<sup>9</sup> investigations, the quantitative relationship between the flow and the electrocardiographic

abnormalities has not been determined. Thus the detection of abnormal ST segment responses can only be qualitatively related to the presumed flow maldistribution. In this study we have used an animal preparation in which clinical electrocardiographic changes can be reproduced<sup>10</sup> to determine whether a quantitative relationship between these two sets of variables exists. We asked two specific questions. First, is there a specific degree of transmural redistribution of flow that is required to produce electrocardiographic abnormalities? Second, in the presence of ischemia, is there a direct correlation between the magnitude of the flow redistribution and of the repolarization abnormality?

### Methods

**Experimental preparation.** We successfully studied 19 adult mongrel dogs. All underwent a left thoracotomy under sterile conditions and with an anesthesia mixture of halothane, nitrous oxide, and oxygen. A quadripolar plaque electrode was sutured to the right atrial appendage and a plastic catheter was inserted into the left atrium. No other procedure was performed in five control dogs (group A).

In the remaining 14 dogs (group B), an ameroid constrictor<sup>11</sup> with an internal diameter of 2.77 mm was placed around the proximal left circumflex coronary artery. This device produces

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progressive arterial obstruction, with complete occlusion occurring after approximately 3 weeks.<sup>3, 4, 10</sup> The constrictor was placed proximal to all ventricular branches in each case.

Lead wires and the atrial catheter tubing were tracked to the back of the neck and buried. The chest wall was closed in layers, air was evacuated under a water seal, and the dogs were permitted to recover.

**Experimental protocol.** Three weeks after surgery, when all animals were ambulatory and well, electrocardiographic and regional myocardial blood flow data were recorded. First, animals were sedated with Innovar-Vet (20 mg of fentanyl and 0.4 mg of droperidol per milliliter). Second, lead wires and the left atrial catheter were exteriorized. Third, a large bore catheter was placed into a femoral artery and advanced into the abdominal aorta for withdrawal of arterial blood. Fourth, 84 chloridized silver electrodes were secured to the animal's shaven chest, in 14 columns of six electrodes each. Two-thirds of these were placed on the anterior and one-third on the posterior aspects of the chest, extending from the level of the clavicles to below the rib margins. Additional electrodes were fixed to the extremities to record limb leads and to derive a Wilson central terminal voltage.

Electrocardiographic signals were amplified by variable gain (1 to 16,000) differential amplifiers (electrode vs Wilson central terminal potential), and digitized at a rate of 500 samples per channel per second. Amplifiers had a bandpass ( $-3$  dB) of 0.04 to 1500 Hz. Voltages from all electrodes were sampled simultaneously.

Fourteen seconds of electrocardiographic data were acquired during spontaneous sinus rhythm and during atrial pacing. Pacing was initiated at the lowest rate capable of maintaining atrial capture, usually 90 beats/min, and increased by 20 beats/min at 4 min intervals until a peak rate of 210 beats/min was reached. Stimuli were 2 msec in duration and 25% over threshold in amplitude. Atropine (0.2 to 1.0 mg) was administered intravenously if second-degree atrioventricular block developed. Electrocardiographic signals were recorded during the last minute at each paced rate.

Exercise could not be used to produce tachycardia because of the body motion and the electrical noise produced by the motor-driven devices, both of which would interfere with the multi-channel electrocardiographic recordings. However, as shown by Fedor *et al.*,<sup>8</sup> for example, pacing produces at least as great a metabolic stress as does exercise.

Radiolabeled microspheres were injected into the left atrium after 3 min of pacing at rates of 90, 150, 170, 190, and 210 beats/min. Spheres were labeled with <sup>46</sup>Sc, <sup>153</sup>Gd, <sup>113</sup>Sn, <sup>103</sup>Ru, or <sup>57</sup>Co (New England Nuclear) and measured  $9 \pm 1$   $\mu$ m in diameter. At each rate, approximately 3 million spheres, suspended in 10% dextran with polysorbate 80 added, were injected and the catheter was flushed with 10 ml of warmed saline over 10 sec. Before administration, vials were agitated vigorously for at least 1 min. Arterial blood was withdrawn from the previously placed abdominal aortic catheter at a rate of 8.0 ml/min, beginning 30 sec before and ending 90 sec after microsphere injection.

**Myocardial blood flow measurements.** Immediately after completion of the pacing protocol, we anesthetized the dogs with pentobarbital and rapidly excised their hearts. The cut end of the aortic root was attached to one perfusion cannula. A second cannula was inserted into the left circumflex artery immediately distal to the ameroid constrictor (group B) or at the corresponding site for control animals in group A. Complete occlusion of the circumflex artery within the ameroid constrictor was verified visually in dogs of group B. The aortic root and the circumflex vessel were next perfused by red and blue dyes (Dupont, Inc.), respectively, at equal perfusion pressures of 100

mm Hg for at least 2 min to define the circumflex perfusion bed.<sup>12</sup> The hearts were then placed in buffered formalin.

After fixation, the hearts were cut into 8 ml thick slices parallel to the atrioventricular ring with a brain macrotome. Slices were photographed, and the percentage of the left ventricle in each slice that was stained blue was computed by a microcomputer-based graphic digitizing tablet. The sum of such areas in all slices represented the percentage of the left ventricle perfused by the left circumflex coronary artery.

A full-thickness section from the center of the circumflex perfusion bed in each of two midlevel slices was subdivided into endocardial, middle, and epicardial thirds. A second set of three samples was cut from the anterior paraseptal zone, corresponding to the perfusion territory of the anterior descending coronary artery.<sup>12</sup> Each piece was weighed and the radioactivity was counted (LKB CompuGamma). Software routines subtracted background and corrected for overlap of the energy spectra of the five isotopes. Reference arterial blood samples were similarly counted.

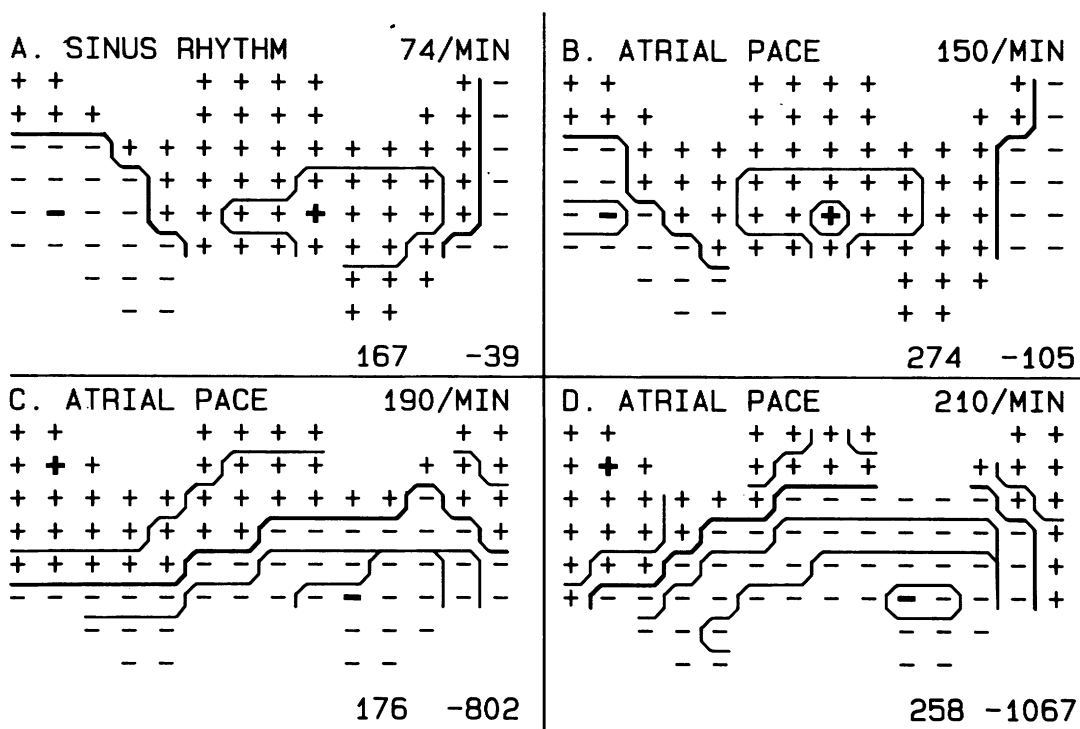
Myocardial blood flow per gram of tissue was then computed by the equation:  $Q_m = Q_r C_m / C_r W_m$ , where  $Q_m$  = myocardial blood flow (ml/g),  $C_m$  = counts per minute in myocardial sample,  $C_r$  = counts per minute in reference arterial sample,  $Q_r$  = flow rate of reference arterial sample (ml/min) and  $W_m$  = weight (mg) of myocardial specimen.<sup>13</sup> The endocardial-to-epicardial (endo/epi) flow ratio in each slice was calculated as the ratio of the flow in the endocardial third to that in the epicardial third. Values from each of the two slices studied for each heart were then averaged; in no case did the two values differ by more than 10%.

**Electrocardiographic recordings.** Electrocardiographic data were processed as previously described.<sup>10</sup> First, six to 10 PQRSST waveforms in each lead with stable baselines and with similar morphologies, as determined by an automated autocorrelation routine,<sup>14</sup> were averaged to reduce random noise. Next, onsets and offsets of the P wave, the QRS complex, and the T wave were selected manually from plots of three relatively orthogonal leads. A 10 msec period of the terminal PR segment was selected and averaged for use as a zero potential baseline.

Finally, body surface isopotential distributions were constructed from potentials recorded at 4 msec intervals during the ST segment. Isopotential maps were drawn connecting points at equal potential relative to the instantaneous Wilson central terminal voltage. At high pacing rates the stimulus artifact of one cycle was superimposed on the ST-T wave of the preceding waveform; only portions of the ST segment before this overlap were evaluated.

Isopotential "difference" maps were also drawn. We constructed these by subtracting voltages recorded at each torso site during sinus rhythm from those at the same site at each pacing rate. The resultant distribution corrected for differences in control patterns and, in effect, depicted the electrical field "generated" by the intervention, i.e., atrial pacing.

**Data analysis and statistics.** Body surface isopotential distributions at each pacing rate were classified as representing a normal or an ischemic pattern, based on previously reported criteria.<sup>15</sup> One example of this assignment is shown in figure 1. Data from one dog recorded 3 weeks after implantation of the ameroid constrictor are shown. In each isopotential map, plus and minus signs correspond to electrode locations, with the sign indicating the polarity of the sensed voltage. The center of each map is along the sternum, with the right and left margins lying on the left and right parasternal borders, respectively. Contour lines connect loci at equal potential relative to the Wilson central terminal voltage. Magnitudes of the maximum (most positive) and of the minimum (most negative) potential in each pattern are tabulated.



**FIGURE 1.** Body surface isopotential distributions, constructed from voltages registered 40 msec into the ST segment, from one dog 3 weeks after implantation of an ameroid constrictor around the left circumflex coronary artery. The center of each map is along the sternum, with the left and right edges corresponding to the right and left paravertebral zones, respectively. Plus and minus signs mark electrode locations, with the sign corresponding to the polarity of the sensed voltage. Contour lines connect sites at equal potential relative to the Wilson central terminal. Large plus and minus signs mark positions of the maximum and minimum, and the zero potential contour is overdrawn for emphasis. A, Pattern at 74 beats/min, with contour lines at 0 and at  $\pm 100 \mu\text{V}$ . B, At 150 beats/min, with contour lines at 0 and at  $\pm 100$  and  $200 \mu\text{V}$ . C, At 190 beats/min, with contour lines at 0 and at  $\pm 100$  and  $400 \mu\text{V}$ . D, At 210 beats/min, with contour lines at 0 and at  $\pm 100$ ,  $400$ , and  $1000 \mu\text{V}$ . The maximum and minimum voltages are tabulated in each panel. Patterns in panels A and B are normal responses to rates; those of panels C and D reflect subendocardial ischemia.

During sinus rhythm, at a rate of 74 beats/min, the pattern 40 msec (figure 1, A) into the ST segment is dominated by an anterior maximum ( $167 \mu\text{V}$ ) surrounded by lateral and posterior negativity. When rate was increased by atrial pacing to 150 beats/min (figure 1, B), the overall pattern remained like that at rest, while the magnitudes of both extrema increased progressively. This pattern was observed in all control animals at rates up to 210 beats/min and in dogs with ameroid constrictors at lower pacing rates.

At rates of 170 beats/min and higher, isopotential patterns (figure 1, C and D) in dogs with ameroid constriction demonstrated new and abnormal negative voltages over the anterior caudal torso. These potentials correspond to ST segment depression in scalar recordings from unipolar leads in this region and are considered to represent tachycardia-induced subendocardial ischemia.<sup>6</sup>

Maps from all data sets with features like those of figure 1, A and B, were classified as normal. Those similar to the maps in figure 1, C and D, were categorized as ischemic. This classification was performed during review of isopotential distributions in a random sequence, without knowledge of the pacing rate or coronary artery status. This type of classification scheme based on spatial patterns obviates the effects of lead axis and time dependency<sup>15</sup> as well as torso size and shape, etc., which would confound detection of abnormalities based on discrete quantitative levels.

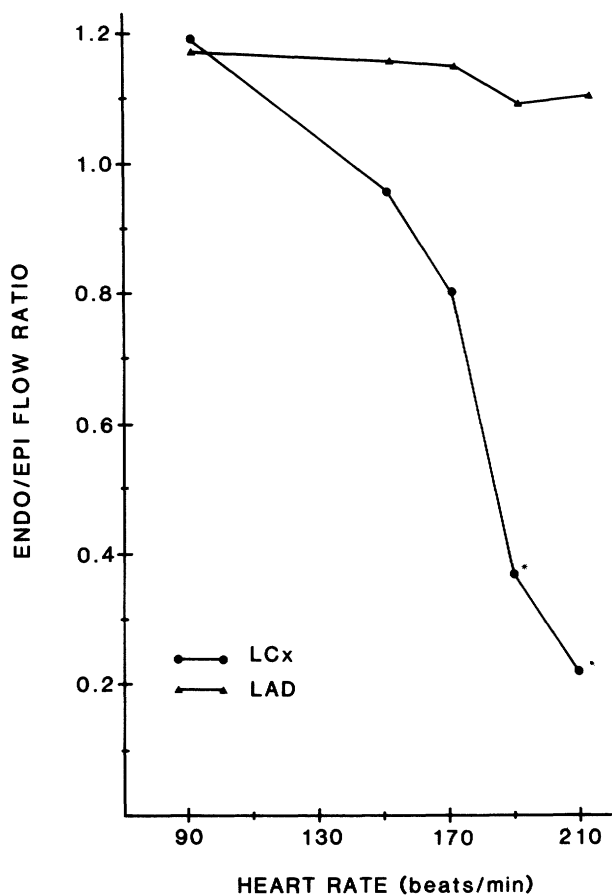
All data are presented as mean  $\pm 1$  SD. Descriptive statistics

of and correlations between electrocardiographic and blood flow variables were computed by standard automated statistical methods,<sup>16</sup> relying on a 1% level of statistical significance.

Factors that were significant and independent predictors of an abnormal electrocardiographic pattern were determined using a stepwise logistic regression analysis.<sup>16</sup> The coded isopotential map pattern was entered as the dependent variable, and the endo/epi flow ratio, heart rate, and percentage of the left ventricle perfused by the circumflex artery were independent variables. The latter factors were added to ( $p < .10$ ) or deleted from ( $p > .15$ ) the regression model in a stepwise manner based on an iterative maximum likelihood ratio method. After determination of the optimal set of independent variables, all cases were assigned to normal or abnormal groups based on the calculated logistic function with a jackknifed classification scheme.

## Results

**Myocardial blood flow.** In the five control dogs of group A, pacing to rates of 210 beats/min did not significantly alter the transmural distribution of myocardial blood flow. The endo/epi flow ratios in the circumflex bed equaled  $1.18 \pm 0.17$  during sinus rhythm ( $71 \pm 11$  beats/min) and  $1.11 \pm 0.12$  at a paced rate of 210 beats/min. The difference in each



**FIGURE 2.** One example of the effect of incremental atrial pacing on transmural myocardial flow 3 weeks after implantation of an ameroid constrictor about the left circumflex artery. Endocardial/epicardial (endo/epi) flow ratios for the nonischemic left anterior descending (LAD) and for the jeopardized left circumflex (LCx) perfusion beds are shown. Tachycardia produced flow redistribution in the LCx but not in the LAD territory. At rates of 190 and 210 beats/min (asterisks), an ischemic electrocardiographic response was recorded.

animal was  $0.08 \pm 0.04$  and was not statistically significant (paired *t* test,  $p > .1$ ). Similarly, flow in the anterior descending perfusion territory was not altered; endo/epi ratios changed by  $0.07 \pm 0.06$  ( $p > .1$ ). Thus rapid pacing did not alter flow patterns in dogs with normal coronary arteries.

In dogs studied after ameroid constriction (group B), pacing likewise did not alter transmural flow in the left anterior descending coronary artery or nonischemic bed. One example is shown in figure 2. Endo/epi flow ratios changed from  $1.09 \pm 0.17$  at a rate of 90 beats/min to  $1.11 \pm 0.11$  at a paced rate of 210 beats/min.

Major changes in circumflex or ischemic bed perfusion did, in contrast, result from atrial pacing. The ischemic bed occupied  $36.31 \pm 6.52\%$  of the left ventricle. The endo/epi flow ratio in this bed at 90

beats/min measured  $1.16 \pm 0.15$ ; this value was not different from that in the nonischemic bed ( $p > .1$ ) and not different from the circumflex bed of control (group A) animals ( $p > .1$ ).

In 11 of the 14 dogs of group B, significant redistribution of transmural blood flow occurred in the ischemic bed with atrial pacing. One example is shown in figure 2. Endo/epi flow ratio fell from 1.22 to 0.18 with an increase in rate from 90 to 210 beats/min. The endo/epi ratio at peak paced rate varied from 1.28 to 0.18; in the 11 cases that did exhibit redistribution, the range was 0.41 to 0.18 at 210 beats/min. The reduction in endo/epi ratio was, as previously reported,<sup>3, 4, 8</sup> caused by a decrease in endocardial flow ( $p < .01$ ) without a significant change in epicardial perfusion.

Thus 11 of 14 (79%) dogs developed selective, regional flow redistribution during atrial pacing.

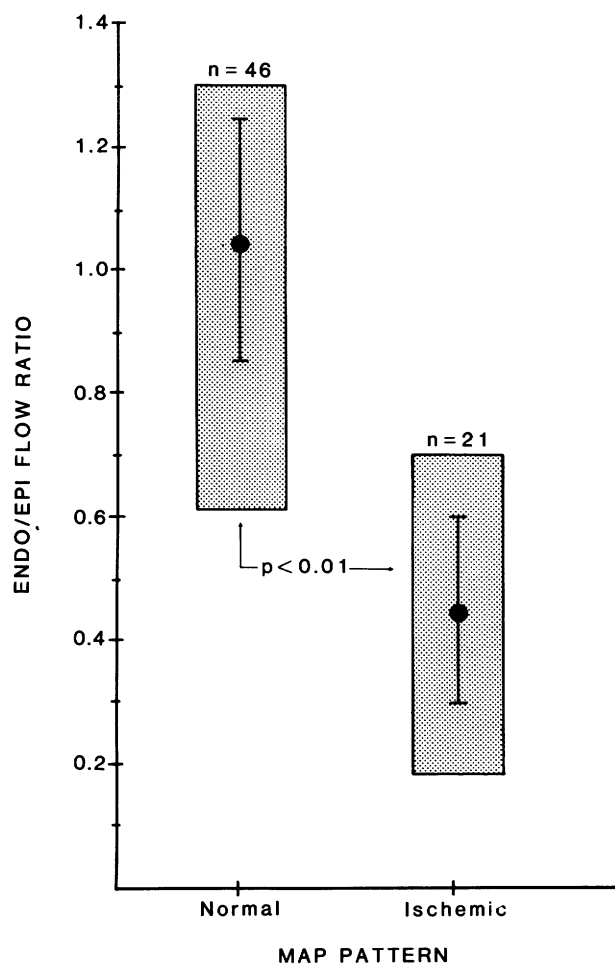
**Electrocardiographic changes.** Isopotential distributions, 20 to 40 msec into the ST segment, were normal in control dogs during sinus rhythm as well as at all pacing rates. None developed changes of myocardial ischemia.

In 11 of 14 dogs in group B, studied 3 weeks after implantation of the ameroid constrictor, ischemic patterns were recorded at paced rates of 170 to 210 ( $184.0 \pm 16.5$ ) beats/min. These were the same 11 that demonstrated flow redistribution. Of 67 electrocardiographic-flow data sets examined in these animals, 46 (68.7%) were categorized as normal and 21 (31.3%) were classified as ischemic. In all 11 animals, the ischemic pattern was as depicted in figure 1 and was consistent as previously reported<sup>17</sup>; potential magnitudes varied but overall topography did not vary from animal to animal.

Isopotential patterns 20 and 40 msec into the ST segment (measured from QRS offset) were examined; in each case, the classification at each instant was the same. Therefore data recorded 40 msec into the ST segment were used for further analysis.

**Electrocardiographic flow correlations.** The major goal of this study was to relate the electrocardiographic changes described above to the concomitant regional blood flow alterations. A total of 67 data sets with adequate electrocardiographic and flow measurements were studied; three others were rejected because of absence of an identifiable ST segment without pacemaker artifact or P wave superposition. First, we compared flow ratios associated with normal and with ischemic electrocardiographic responses. The range of endo/epi flow ratios from data sets of normal and of ischemic responses are depicted in figure 3. Ratios with normal potential patterns measured  $1.05 \pm 0.19$ ,





**FIGURE 3.** Endocardial/epicardial (endo/epi) flow ratios associated with normal (left) or ischemic (right) body surface isopotential patterns. Boxed areas indicate ranges for each subset, with mean and  $\pm 1$  SD values drawn within. The number of cases in each set (n) is indicated. Flow ratios were significantly lower ( $p < .01$ ) with ischemic than with normal repolarization responses.

whereas those with ischemic isopotential patterns equaled  $0.45 \pm 0.15$ . These values were significantly different ( $p < .001$ , unpaired t test). Thus ischemic electrocardiographic patterns were associated with lower endo/epi flow ratios than were nonischemic responses. The endo/epi ratio at the lowest heart rate producing an abnormal ST segment pattern in each dog was  $0.53 \pm 0.16$  (0.18 to 0.69).

Next, we attempted to determine which if any measured variables were independent predictors of an ischemic ST segment response. To do so, we used a stepwise logistic regression analysis. Independent variables considered were heart rate and the percentage of the left ventricle perfused by the obstructed circumflex artery, in addition to the transmural flow ratio. Only the endo/epi flow ratio was selected as significant predictive variable for separating the two electrocar-

diographic responses ( $p < .01$ ). Neither rate nor bed size added to the discriminating ability of this value.

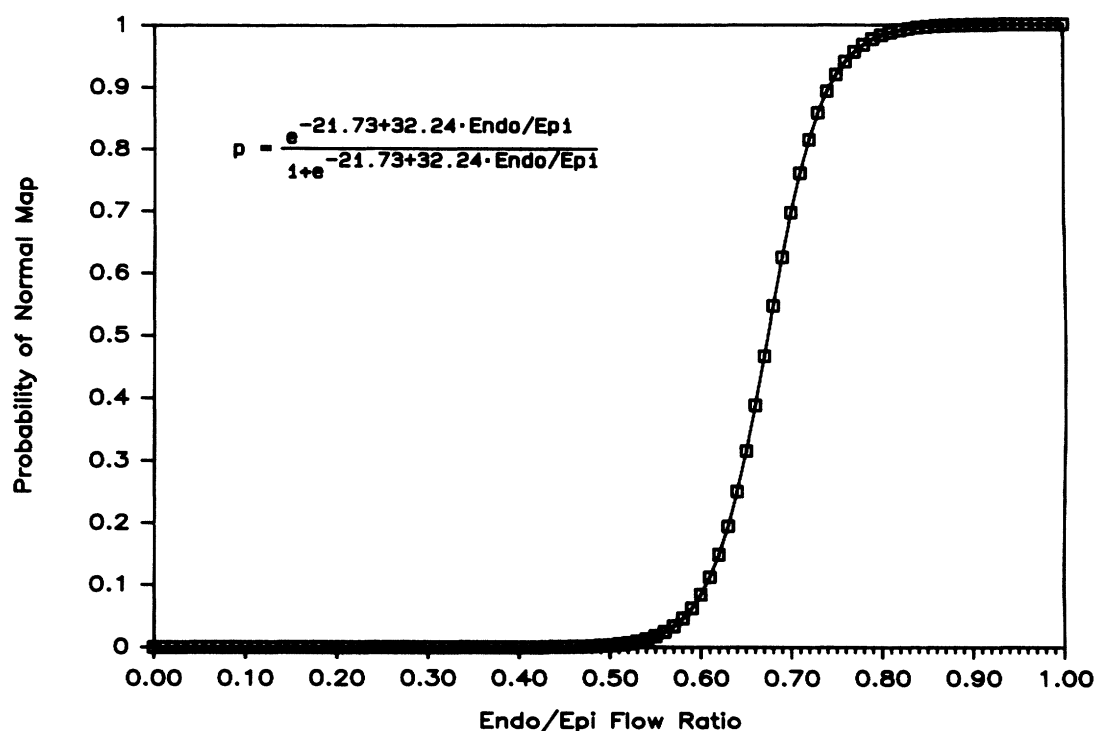
A plot showing the probability of observing a normal electrocardiographic pattern (y-axis) with endo/epi ratios of 0.0 to 1.0 (x-axis) is shown in figure 4. This relationship was derived from the computed logistic regression equation tabulated in the figure. As can readily be seen, a sharp demarcation between near zero and near unity probabilities occurred at endo/epi ratios of 0.57 and 0.70. An equal likelihood of a normal and an ischemic response was observed at an endo/epi ratio of 0.67. Ratios of 0.58 and 0.76 predicted abnormal or normal patterns, respectively, with probabilities of 95%.

A simple classification scheme based on this probability function accurately predicted 95.5% of cases. Only three responses were inaccurately predicted by this single variable statistical model; all three were normal patterns incorrectly classified as ischemic ones. This corresponded to a sensitivity of 100% and a specificity of 93.5%.

Finally, we attempted to determine whether the magnitude of the ST segment shift correlated with the magnitude of the transmural flow abnormality. To do so, only data from the 11 dogs that developed the abnormal ST shifts to be evaluated were studied. First, we constructed isopotential difference maps by point-by-point subtraction of potentials recorded during sinus rhythm from those sensed at higher pacing rates. This served to normalize differences in the resting ST potential; maxima at rest did range from 89 to  $248 \mu\text{V}$ . Use of early ST time points reduced the effect of sampling at different relative times during ventricular recovery as rate increases.<sup>18</sup> Next, the peak negative potential in each map was correlated with the concomitant flow value. Results are shown in figure 5. A significant ( $p < .01$ ) negative correlation existed between the endo/epi flow ratio and the magnitude of ST segment abnormality. The regression equation, tabulated in the figure, then quantitatively related the two data types. Size of the perfusion bed was not correlated with ST shift ( $r = .11$ ).

## Discussion

This experimental study demonstrated two related phenomena. First, the onset of abnormal ST segment shifts in an animal preparation of transient myocardial ischemia did correspond to a critical degree of myocardial blood flow redistribution. Second, the intensity of that repolarization shift was highly correlated with the magnitude of the flow redistribution. These findings may be considered in the context of (1) the methods



**FIGURE 4.** Probability (*p*) of observing a normal isotential map, 40 msec in to the ST segment, for endo/epi flow ratios of 0.0 to 1.0, as predicted from the listed logistic regression equation. A 50% probability was predicted with a flow ratio of 0.67.

and preparations used, (2) prior studies of flow and electrocardiographic changes in this and related experimental preparations, and (3) possible implications to clinical exercise stress testing.

**Ameroid constriction.** Ameroid constriction of the left circumflex artery represents a preparation of progressive arterial obstruction without significant myocardial infarction.<sup>19</sup> Complete occlusion occurs 17 to 25 days after implantation in experimental studies.<sup>3, 4, 7</sup> However, total flow at rest in the subserved vascular bed remains normal or near normal during acute and chronic phases because of parallel increases in collateral flow.<sup>4</sup> Tissue viability<sup>19</sup> and myocardial function at rest<sup>3, 4</sup> are thereby maintained. These findings are as described in our animals; circumflex bed endo/epi flow ratios at rest were normal.

Although this collateral recruitment and/or growth maintains flow and function at rest, hypoperfusion and myocardial dysfunction occur with metabolic stress. Whereas in normal dogs, tachycardia produces a homogeneous increase in coronary blood flow,<sup>4</sup> in animals with coronary obstruction significant endocardial underperfusion results.<sup>4, 8, 20</sup> In our studies, endo/epi flow ratios in the circumflex bed decreased from over unity to 0.41 to 0.18 in 11 of 14 dogs. That all animals did not demonstrate this redistribution is consistent with the heterogeneous response to exercise emphasized by Fedor *et al.*<sup>8</sup> and by Bache and Schwartz.<sup>20</sup>

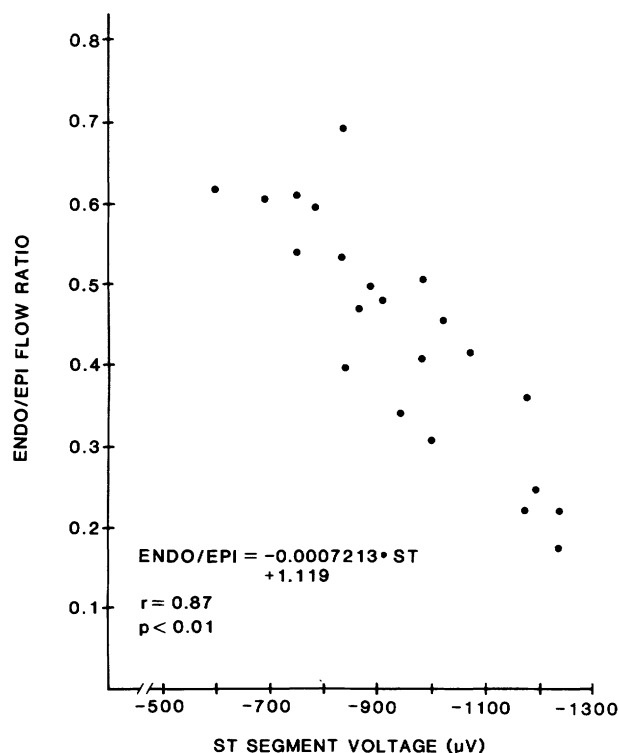
Thus our flow data are as previously reported in this animal preparation.

Subendocardial ischemia, such as produced by pacing in this ameroid constrictor preparation, produces ST segment depression in epicardial and body surface electrocardiograms.<sup>6</sup> Such shifts reflect reversal of the normal transmural gradient of ventricular recovery times caused by subendocardial ischemia.<sup>5</sup>

Previous studies from this laboratory have sought to define the variables governing the body surface expression of this electrophysiologic effect. We have demonstrated that the development and torso distribution of ST depression is dependent on location of the lesion<sup>17</sup> and on the ventricular activation sequence.<sup>18</sup>

**Electrocardiographic-flow correlations.** The current study was undertaken to expand these prior efforts by correlating the observed electrocardiographic responses with the presence and extent of flow redistribution caused by tachycardia. Studies after acute coronary obstruction have demonstrated that ST segment elevation occurs only after at least a 50% reduction in flow<sup>21, 22</sup> and that a general correlation exists between the magnitude of the flow deprivation and intramyocardial gas tensions and the ST response, although wide scatter is seen.<sup>23-26</sup> A similar relationship between flow and epicardial/endocardial electrograms was reported by Ruffey *et al.*<sup>27</sup>

In contrast to these studies of supply-side ischemia,



**FIGURE 5.** Relationship between endo/epi flow ratio and the magnitude of ST segment (40 msec) minimum in ischemic isopotential difference patterns. The regression equation, correlation coefficient ( $r$ ), and  $p$  value for the significant relationship are tabulated.

evaluation of ischemia produced by increased demand are limited. Guyton et al.<sup>6</sup> produced ischemia by pacing after ameroid constriction; endocardial ST elevation and epicardial ST depression both increased progressively as distal perfusion pressure was reduced from 100 to 50 mm Hg.

The two major findings of this study amplify and extend these prior observations. First, as shown in figure 2, an ischemic isopotential pattern was associated with an endo/epi flow ratio of 0.69 or less. As demonstrated by the logistic regression model, this one variable correctly predicted the electrocardiographic pattern in over 95% of cases. The sharp break in the flow ratio (figure 4) between normal and abnormal repolarization responses suggests a threshold phenomenon. The exact value of such an effect may be inaccurate, since recordings and measurements were made intermittently rather than continuously during the pacing protocol. It may also have varied if compared with contraction and/or metabolic measures, which may be more sensitive indicators of ischemia.<sup>28</sup> Lesion size, in contrast, was not independently predictive of the ST pattern.

Prior experimental<sup>29, 30</sup> and clinical<sup>31, 32</sup> studies have suggested that mechanical dysfunction is also general-

ly correlated with flow and may be a more sensitive marker of myocardial ischemia than are ST segment shifts. A direct comparison between level of flow deprivation required to produce each abnormality, while technically feasible, has not been done. It may be anticipated, however, that functional changes may occur at a higher threshold level than do electrocardiographic changes.

Second, the intensity of the ST shift directly correlated with the magnitude of the ischemic response as measured by the transmural flow ratio. Here also, lesion size was not correlated with the quantitated repolarization abnormality.

That intensity of ischemia should be a major determinant of ST shift may be anticipated from the solid angle theorem<sup>33</sup> as well as from equivalent generator models.<sup>34</sup> Both formulations permit quantitation of electrical potential at a point in or on the surface of a volume conductor as the product of two terms — one defining the geometry of the electromotively active surface and one reflecting the intensity of current flux across its boundaries. The former may be termed spatial and the latter nonspatial variables.

Data in figure 5 emphasize the importance of the nonspatial, intensity-related factors in generating ST segment depression. The magnitude of the repolarization abnormality increased as the endo/epi flow ratio decreased, reflecting the intensity of ischemia. The lack of correlation of the ST response to bed size, an effect not predicted by the solid angle theorem, is likely a reflection of the study of a single vascular bed in a relatively narrow range of sizes. Under such conditions, however, intensity factors do play a major role in determining the ST segment response.

**Clinical implications.** Both findings indicating a quantitative relationship between flow and electrocardiographic responses to myocardial ischemia provide a physiologic basis for interpreting the exercise<sup>1</sup> or paced<sup>2</sup> electrocardiogram. The previously reported correlation between ischemic isopotential patterns used here and simple ST segment depression<sup>15</sup> used clinically permits this link. First, an abnormal ST pattern during tachycardia was dependent on achieving a critical degree of flow redistribution. Without it, and despite complete anterograde obstruction, a normal ST pattern was observed. A normal clinical exercise test in the presence of high-grade arterial obstruction may therefore reflect a failure of the stress to provoke the needed degree of flow aberration. A similar conclusion may be derived from the study of regional blood flow in patients with coronary disease reported by Selwyn et al.<sup>9</sup>; ST depression developed only after the onset of

reduced flow, although the quantitative relationship between the two variables was not determined.

Second, the magnitude of the exercise ST shift may be expected to correlate with the intensity of the flow redistribution. However, clinical studies have correlated the magnitude of the ST response to exercise only with the angiographic extent of coronary disease. Weiner *et al.*<sup>35</sup> for example, showed that the incidence of left main or three-vessel coronary disease increased from 24% with 1 to 2 mm of ST depression to 60.1% with greater than 3 mm of shift. Similarly, Cohn *et al.*<sup>36</sup> and others reported that the magnitude and the slope of the depressed ST segment were independent predictors of the anatomic extent of disease.

These and other clinical studies have correlated electrocardiographic variables with the number of vessels involved or the proportion of the left ventricle at risk. These correspond to the spatial factors discussed above. What the present data suggest is that the intensity of ischemia within these vascular beds may play a significant if not the major role in producing the clinical range of ST depression.

Such conclusions must, of course, be tempered by the significant physiologic, pathologic, and anatomic differences between the animal preparation and the human condition. Such variables most probably do alter heart-surface electrocardiographic relationships. But these differences are more likely to alter the specific quantitative results, *e.g.*, the exact regression equations, rather than the concepts that they represent.

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